A Modified Synthesis of 4-Chloromethylthiazoles

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A two-reaction synthesis of 2-substituted-4-chloromethylthiazoles from thioamides and 1,3-dichloroacetone is reported. The first step, cyclization to a 2-substituted-4-chloromethyl-4-hydroxythiazoline is carried out in the presence of bicarbonate in an aprotic solvent. Dehydration of this intermediate to a 2-substituted-4-chloromethylthiazole is accomplished by reaction with thionyl chloride, sulfuryl chloride, phosphoryl chloride, phosphorus trichloride or phosphorus pentachloride. Substituents on the thioamide, such as amino, alkyl, or aryl, are shown not to affect the success of the reaction. As a trend, alkylthioamides give slightly better yields of 4-chloromethylthiazoles than do arylthioamides. The yields of 4-chloromethylthiazoles prepared using this procedure are comparable to the yields obtained using acid catalyzed procedures.

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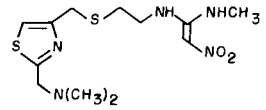
Nizatidine (**1**) has been reported [1] to be a powerful H_2-receptor antagonist useful in the treatment of peptic



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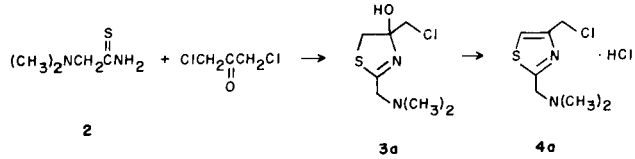
ulcer. Synthesis of **1** required as an intermediate 2-(*N,N*-dimethylaminomethyl)-4-chloromethylthiazole (**4a**). Historically, 2-substituted-4-chloromethylthiazoles have been prepared by reaction of 1,3-dichloroacetone and the appropriate thioamide under acidic conditions [2-8]. The reaction proceeds through an intermediate 4-hydroxy-4-chloromethylthiazoline [9], which either dehydrates spontaneously under the reaction conditions [4,6] or on addition of a suitable acid catalyst, such as concentrated hydrochloric acid [2,5], zinc chloride [3], acetic acid [7], or cold concentrated sulfuric acid [8]. More recently, others have reported the synthesis of thiazoles using phosphorus oxychloride [10] or acetic anhydride [11] as dehydrating agent.

In our synthetic investigations, however, reaction of amino-substituted thioamides such as *N,N*-dimethylaminothioacetamide (**2**) under these acidic conditions was unsuccessful. The thioamide would precipitate from solution as its hydrochloride salt and would not react further. Novel reaction conditions which would successfully convert thioamides of this type to 4-chloromethylthiazoles were therefore pursued. As a result of these studies, a useful route to 2-amino-substituted 4-chloromethylthiazoles has been developed and alternative conditions for the dehydration of the intermediate 4-hydroxy-4-chloromethylthiazolines have been elaborated.



2 **3a** **4a**

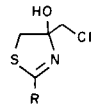
Reaction of **2** with 1,3-dichloroacetone in a non-protic solvent resulted in the formation of some **3a** and hydrogen chloride. The starting thioamide **2** acted as an acid scavenger and precipitated from solution as its hydrochloride salt, effectively stopping the reaction. Switching to a protic solvent or a polar-aprotic solvent such as dimethylformamide improved the solubility of the hydrochloride salt, but also greatly increased undesirable side reactions. It was found that the reaction could be run in a non-protic solvent if one equivalent of sodium or potassium bicarbonate was added to the reaction mixture. The bicarbonate effectively scavenged the hydrogen chloride generated during the ring closure, allowing **2** to remain in solution and react further. While the reaction never went to completion, approximately 95% of **2** was converted to **3a** in 24 hours. Longer reaction times resulted in polymeric degradation of **3a** which is relatively unstable in solution [12].

Other bases, such as sodium carbonate, pyridine, triethylamine, sodium sulfite, sodium dihydrogen phosphate, and dimethylaniline were used in place of bicarbonate without success. Bases of a pK_b greater than bicarbonate reacted with the 1,3-dichloroacetone; bases of a pK_b less than or equal to bicarbonate had no effect. Excess bicarbonate did not interfere with the reaction. As an alternative procedure, the hydrochloride salt of **2** was used successfully in the reaction as long as sufficient excess bicarbonate was used to scavenge the extra equivalent of hydrogen chloride present. Because of this proton exchange between **2** and the bicarbonate, reaction solvent choice was determined by the requirement that the hydrochloride salt of **2** be at least partially soluble. Solvent choice was further constrained by the subsequent dehydration reaction which required a non-protic solvent.

This procedure for conversion of thioamides to 2-substituted-4-chloromethyl-4-hydroxythiazolines works for a wide scope of substituted thioamides. Substituents such as amino, alkyl, or aryl groups can be present in the starting

Table I

^{1}H-NMR and Elemental Analysis Data for Isolated Compounds



3a-f

4a-f

R	4-Hydroxythiazoline Analysis	^{1}H-NMR δ	4-Chloromethylthiazole Analysis	^{1}H-NMR δ
a) $(CH_3)_2NCH_2$	Theory: [a] C: 40.28, H: 6.28, N: 13.42 Found: C: 40.54, H: 6.13, N: 13.29	2.4 (6H, S), 3.40 (4H, M), 3.8 (2H, S), D_6-DMSO & deuteriochloroform	Theory: [b] C: 37.01, H: 5.32, N: 12.33 Found: C: 37.07, H: 5.20, N: 12.10	3.0 (6H, S), 4.9 (4H, S), 7.9 (1H, S) deuterium oxide
b) CH_3	Theory: [b] C: 29.72, H: 4.49, N: 6.93 Found: C: 29.94, H: 4.32, N: 6.89	2.6 (3H, S), 3.8 (2H, Q), 4.05 (2H, S) D_6-DMSO	Theory: [b] C: 32.62, H: 3.83, N: 7.61 Found: C: 32.74, H: 4.02, N: 7.40	2.9 (3H, S), 4.7 (2H, S), 7.7 (1H, S) deuterium oxide
c) C_6H_5	Theory: [b] C: 45.47, H: 4.20, N: 5.30 Found: C: 45.66, H: 4.26, N: 5.26	3.75 (2H, Q), 4.1 (2H, S), 7.8 (5H, M) D_6-DMSO	Theory: [b] C: 48.79, H: 3.69, N: 5.69 Found: C: 48.53, H: 3.71, N: 5.52	5.0 (2H, S), 7.6 (4H, M), 8.2 (2H, M), 11.3 (1H, S) deuteriochloroform
d) 2-Thienyl	Theory: [b] C: 35.56, H: 3.36, N: 5.18 Found: C: 35.82, H: 3.58, N: 4.90	3.7 (2H, Q), 4.0 (2H, S), 8.0 (3H, M) D_6-DMSO	Theory: [a] C: 44.54, H: 2.80, N: 6.49 Found: C: 44.78, H: 2.51, N: 6.36	4.65 (2H, S), 7.2 (4H, M) deuteriochloroform
e) $CH_3(CH_2)_6$	Theory: [b] C: 46.15, H: 7.39, N: 4.89 Found: C: 46.44, H: 7.34, N: 4.83	0.7-2.1 (13H, BM), 3.0 (2H, M), 4.0 (4H, Q & S) deuteriochloroform	Theory: [b] C: 49.25, H: 7.14, N: 5.22 Found: C: 49.38, H: 7.36, N: 5.01	0.7-2.1 (13H, BM), 3.05 (2H, T), 4.7 (2H, S), 7.2 (1H, S) deuteriochloroform
f) Pyrrolidinomethyl	[c,d]	[c]	[d,e]	1.8 (4H, M), 3.3 (4H, M), 4.75 (2H, S), 4.95 (2H, S), 7.8 (1H, S) D_5-Pyridine

[a] Free base. [b] HCl salt. [c] Compound would eliminate to thiazole on isolation. [d] Satisfactory elemental analysis could not be obtained for this compound. [e] Exact mass spectroscopy gave for (M + 1) = 217.0548, theory is 217.0566.

thioamide without affecting the success of the reaction. Table I lists examples of thioamides that have been converted to 2-substituted-4-chloromethyl-4-hydroxythiazolines (and eventually to 2-substituted-4-chloromethylthiazoles) using these conditions. Generally, the 2-substituted-4-chloromethyl-4-hydroxythiazolines could be isolated analytically pure by precipitation from solution as the hydrochloride salt.

Having successfully formed the 2-substituted-4-chloromethyl-4-hydroxythiazolines, dehydration to the corresponding 2-substituted-4-chloromethylthiazoles was investigated. Conversion of **3a** (unisolated from the first reaction except for filtration from the insoluble inorganic salts) to **4a** could not be accomplished by acid catalysis. Addition of acids such as hydrochloric acid, sulfuric acid, anhydrous hydrogen chloride, acetic acid, and *p*-toluenesulfonic acid to **3a** either gave no reaction or extensive decomposition of the starting material. Other elimination techniques were therefore tried. Reaction of **3a** with phosgene, oxalyl chloride, or oxalyl chloride in DMF resulted in extensive decomposition of the starting material. Thionyl chloride, phosphorus trichloride, phosphorus pentachloride, phosphorus oxychloride, and sulfuryl chloride, however, all gave fairly clean dehydra-

Table II

Effect of Dehydrating Reagent on Yield
Of Conversion of **3a** to **4a**

Dehydrating Reagent	Equivalents Used	% Theory Yield
Phosphorus pentachloride	2.2	87.5 [b]
Phosphoryl chloride	3.3	69.8 [a]
Thionyl chloride	1.1	75.8 [a,c]
Sulfuryl chloride	1.1	60.2 [a,c]
Phosphorus trichloride	3.3	94.1 [b]

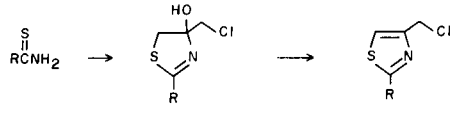
[a] Yield calculated from isolated solid and corrected for assay by hplc (Zorbax C-8, 50/50 methanol/10m*M* potassium dihydrogen phosphate at *p*H 8, flow rate 1 ml/minute, sample in methanol/water). [b] Product was too hygroscopic for isolation. Product was extracted into water and yield calculated by hplc assay of water solution. [c] Yield was not increased by using more dehydrating agent.

tion of **3a** to **4a**. A comparison of the yields obtained using different dehydrating agents is given in Table II. In each case, an excess of the dehydrating agent was used to react with any water formed during the ring closure that may have remained in the reaction mixture. Thionyl chloride, phosphorus oxychloride, and sulfuryl chloride are the more convenient reagents because **4a** precipitates as its stable hydrochloride salt which can be collected and dried in good yield. Phosphorus pentachloride and phosphorus trichloride offer the advantage of somewhat higher yields, but the precipitated salts are very hygroscopic and contain some phosphorus. For our purposes, the product from these reactions was best isolated by extraction into water. The aqueous extracts were then used directly in subsequent reactions.

As in the first reaction, other basic, alkyl, or aryl substi-

Table III

Conversion of Thioamides to 4-Chloromethylthiazoles



3a-f **4a-f**

R	Reaction Solvent	Cyclization Reaction Time (hours)	Dehydrating Agent	% Theory Overall	Isolation Procedure
a) $(CH_3)_2NCH_2$	1,2-Dichloro-ethane	24	Thionyl chloride	76%	Precipitated from reaction solution as HCl salt. Purified for analysis by recrystallization from HOAc/acetone, mp = 139-141°
b) CH_3	1,2-Dichloro-ethane	48	Thionyl chloride	93%	Reaction solution evaporated and HCl salt crystallized from EtOAc. Purified for analysis by recrystallization from 1,4-dioxane, mp = 168°
c) C_6H_5	1,4-Dioxane	120	Thionyl chloride	79%	Precipitated from reaction solution as HCl salt. No purification required prior to analysis, mp = 141°
d) 2-Thienyl	1,4-Dioxane	48	Thionyl chloride	76%	Precipitated from reaction solution as HCl salt. Purified for analysis and converted to free amine by recrystallization from 1,4-dioxane, mp = 58-60° (lit [7] 54°)
e) $CH_3(CH_2)_6$	1,2-Dichloro-ethane	24	Thionyl chloride	96%	Reaction solution evaporated and residue partitioned between hexane and aqueous bicarbonate. Hexane evaporated to yield free amine. Purified for analysis by prep HPLC (Waters prep 500; silica gel; 2% MeOH, 0.5% HOAc in hexanes; 150 ml/minute)
f) Pyrrolidinomethyl	Chloroform	24	Thionyl chloride	79%	Reaction mixture extracted into water and passed over amberlite IR-120 ion exchange column. Fractions were eluted with water, then 6*N* HCl. Fractions containing product were combined and evaporated.

tuents did not interfere with the dehydration reaction. The generality of this route to 2-substituted-4-chloromethylthiazoles is demonstrated by the examples shown in Table III. As a trend, the data shows that alkylthioamides give slightly better yields of 4-chloromethylthiazoles than do arylthioamides. In most cases, the product was isolated as its hydrochloride salt. This is most convenient as alkyl 4-chloromethylthiazoles tend to dimerize on standing as the free base [3].

The yields of 4-chloromethylthiazoles prepared using this procedure are as good or better than the yields obtained using standard literature procedures. The described procedure is of importance, however, because it can be used to make 4-chloromethylthiazoles with many different substituents with consistent ease. Previous procedures worked inconsistently depending on the nature of the starting material. This new process represents a general method which, with minor changes in solvent, can be used to make most any 4-chloromethylthiazole.

EXPERIMENTAL

All melting points were determined on a Thomas-Hoover capilllary-melting point apparatus and are uncorrected. The nmr spectra were recorded on a Varian T-60 60-MHz spectrometer. Exact mass spectra were obtained using a ZAB-3F mass spectrometer using fast atom bombardment. All solvents were reagent grade and used as purchased. Thioamides that were not commercially available were prepared using the procedure of Taylor and Zoltewicz [13]. All thin layer chromatography was carried out on silica gel using chloroform: methanol:ammonium hydroxide 18:2:0.5 as solvent. Acidic samples were basified first with saturated aqueous sodium bicarbonate prior to tlc. Analytical hplc was performed using a Waters 6000A liquid chromatograph pump and a Waters 440 absorbance detector set at 254 nm. All reactions were run under nitrogen in either 1,2-dichloroethane, 1,4-dioxane, or chloroform. All compounds except *N*-pyrrolidino-4-chloromethylthiazole (**4f**) gave acceptable analyses (see Table I). *N*-Pyrrolidino-4-chloromethylthiazole was characterized by exact mass spectroscopy and proton nmr. For exact reaction conditions see Table III.

General Procedure for the Synthesis of 2-Substituted 4-Chloromethylthiazole Hydrochlorides.

To a 100 ml single neck round-bottom flask equipped with magnetic stir bar and thermometer was added 0.10 mole of thioamide or thioamide hydrochloride, 14.0 g (0.11 mole) of 1,3-dichloroacetone, and 9.3 g (0.11 mole) of sodium bicarbonate (18.5 g or 0.22 mole if the thioamide hydrochloride was used). To this mixture was added 60 ml of solvent. The resultant mix was stirred under nitrogen for 24-48 hours at room temperature. When tlc indicated reaction was essentially complete, the reaction mix was filtered and the filter cake washed with fresh solvent. This filtrate was then added, with cooling, to 0.11 mole of dehydrating agent in 60 ml of solvent maintaining reaction temperature under 30°. The reaction mixture was then heated to 65-70° for thirty minutes. After cooling to room temperture, the product was filtered and the filter cake was washed extensively with fresh solvent. Drying *in vacuo* at 50° yielded pure product. If the product was soluble in the reaction solvent, the solution was evaporated and the product further purified by recrystallization or chromatography as outlined in Table III.

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[12] 2-*N*,*N*-Dimethylaminomethyl-4-chloromethyl-4-hydroxythiazoline, however, can be isolated from solution by evaporation and stored under refrigeration indefinitely.

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